Cell Stem Cell
Forum

Pharma's Developing Interest in Stem Cells

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Human stem cell biology is driving the promise of novel regenerative therapies into clinical trials. Although the pharmaceutical industry has embraced stem cells as tools in drug discovery, few companies have taken the risk to deliver stem cell-based medicines. Here, we evaluate the various cell-based opportunities and corporate strategies.

Recently, pharmaceutical and biotechnology companies have taken an increased interest in stem cell biology. The use of stem cells as research tools has expanded with most of the major pharmaceutical companies using embryonic stem cells (ESCs) or adult stem cells for internal drug discovery programs. These internal efforts are often enhanced through the expertise of external partnerships with academics or biotech companies. The specific use of stem cell-based tools in conventional drug discovery programs are varied but based on the reproducibility of deriving clinically relevant cell types as diverse as sensory neurons, cardiac myocytes, and pancreatic progenitors. Here, rather than focus on the extensive application of the technology as tools for drug discovery, we will discuss the emerging opportunities for biopharmaceutical companies to engage in stem cell-based regenerative medicine. In some instances, the approach will apply the pharmaceutical strength in the research and development of small or large molecules projects to find novel therapeutics that modify endogenous stem/progenitor cell fate. For example, discovery programs that stimulate the endogenous activation of cardiac progenitors for congestive heart failure (CHF) or myocardial infarction (MI) (Wu et al., 2004), expansion of pancreatic islet precursor cells for diabetes (Chen et al., 2009), or activation or release of adult progenitors in immune disorders (Flomenberg et al., 2010). In other cases, autologous or allogeneic adult stem cells are used to induce the body's endogenous regeneration processes in diseased tissue (e.g., ischemia), typically via the action of paracrine factors. Finally, the ultimate promise of stem cell biology is cell/tissue replacement therapy. Cell replacement therapies are anticipated because of the fact that stem cell derivatives may accurately recapitulate the normal biology of cells or tissues and restore function in degenerative diseases. Therefore, we expect that stem cell-based therapeutic approaches will become of particular relevance as pharmaceutical companies seek opportunities in disease modification and away from a focus on purely palliative treatment. As pharmaceutical companies have been working for years with global regulatory agencies and clinical centers to create strong partnerships, this experience is a key strength that the pharmaceutical industry will bring to the Regenerative Medicine space. In this discussion, we have focused on large pharmaceutical companies, (Table 1, note that this analysis is limited to publicly disclosed information), although opportunities for biotech companies could be stronger in autologous cell-based therapies.

Since the earliest protocols using murine ESCs for in vitro differentiation experiments, it was established that small molecules, such as retinoic acid and 5-azacytidine, could be used to direct and modify stem cell fate. The interest in developing drug screens for human ESC differentiation has heightened with better understanding of developmental pathways and the identification of specific molecules to improve cell differentiation (reviewed in Ding and Schultz, 2004). This finding raises the distinct possibility that small and large molecule (e.g., antibodies, nucleotides, proteins) modifiers will also be identified that can enhance endogenous cell and tissue regeneration. As this research paradigm is the strength of biopharmaceutical companies, a commitment to regenerative medicine based on combining drug discovery and stem cell platforms is taking hold across the industry, through internal growth or external partnerships (Trounson et al., 2010, this issue). These new drug discovery opportunities could be applied as stand-alone treatments that induce cell fate (e.g., Erythropoietin) or combined with existing or emerging stem cell-based therapies. Furthermore, the advent of induced pluripotent stem cells (iPSCs) has created an important new opportunity for human pluripotent stem cells carrying specific genetic variants, mutations, and patient specific cell lines to be used in drug discovery and personalized regenerative medicine. (reviewed in Rowntree and McNeish, 2010).

In terms of using stem cells as therapeutics, 68 cell-based approaches are listed under clinical development in a commercial pipeline database. Of these listings, over 90% are company sponsored, with the only large biopharmaceutical companies listed being Teva, Baxter, and Genzyme (Table 2). However, when current/completed clinical studies in four therapeutic areas are evaluated, less than 20% are company sponsored (and only three are large company sponsored), whereas a large number are investigator initiated studies (Table 2). Pharma's involvement may be obscured when there is an equity stake in the small company or if a company sponsors an academic to run the study. Nonetheless, this trend begs the question: why is the pharmaceutical industry hesitant to explore cell-based therapy? Significant factors may include the following: insufficient demonstration

Table 1. Timeline of Large Pharma Activity in Regenerative Medicine

	Drug Modifiers of Stem Cells	Autologous Adult Stem Cells		Allogenic Adult Stem Cells		ESCs/iPSCs	
Company	LC	EI	LC	EI	LC	EI	LC
Pfizer	01/09: ViaCyte (Diabetes)	06/08: Eyecyte (eye)			12/09: Athersys (IBD)		04/09: UCL (eye)
Novartis	03/09: Epistem 11/09: HSCI (CNS)	11/09: Cellerix (GI)	08/09: Opexa (MS)			11/06: ESCs (CNS)	
Roche	06/09: I-STEM (CNS)	11/09: Cellerix (GI)					
Sanofi Aventis	04/10: CureDM (Diabetes)						
Johnson & Johnson		08/05: Tengion (Bladders)			07/02: Neuronyx 06/06: Viacell (CV)	04/07: ViaCyte (Diabetes)	
Amgen		08/03: Viacell (Cord blood bank)					
Novo Nordisk				07/08: Allocure (AKI)			10/08: Cellartis (Diabetes)
Teva (Generics Company)		12/09: MGVS (PVD)	07/05: Proneuron (SCI)		02/05: Gamidacell (Transplant)	09/07: CellCure (eye)	06/07: Technion (ESC)
Medtronic (Device Company)	04/08: Scil (Dental)				11/07: Arteriocyte (Ischemia)		
Smith & Nephew (Device Company)			10/07: REMEDI (Orthopedic)				

Abbreviations are as follows: EI, date of equity investment made in company; LC, date of collaboration or licensing deal made with company; AKI, acute kidney injury; CNS, central nervous system; CV, cardiovascular; GI, gastrointestinal; HSCI, Harvard Stem Cell Institute; IBD, inflammatory bowel disease; MGVA, multigene vascular systems; MS, multiple sclerosis; PVD, peripheral vascular disease; SCI, spinal cord injury; UCL, University College London. Note that Merck, GSK, Abbott, AstraZeneca, Lilly, Bayer, BMS, Takeda show no public activity pursuing cell-based therapeutics, but most are pursuing stem cells as tools for enabling R&D. Source: EvaluatePharma (5/09 and generics excluded from Rx) for 2014 revenue projections and data on Regenerative Medicine activity from public data searches primarily from company websites.

of efficacy, regulatory, and safety concerns; a belief that cell therapies will not offer substantial benefit over existing therapies or demonstrate uptake by patients; and lack of familiarity with both the business model for commercializing cell-based products and the complexity of developing a product. Therefore, to date, few large pharmaceutical companies are actively conducting clinical trials given the challenges outlined above. For pharmaceutical companies to move into the commercialization of cellular regenerative medicine products, a ''tipping point'' needs to be reached, and the barriers facing this industry will be dependent on the type of cell-based approach under development.

Of the existing clinical trials using stem cells (Table 2), the majority have relied and continue to rely on autologous cells, for example, the patients' own bone marrow-derived mesenchymal stromal cells (MSCs). This therapeutic approach typically focuses on cellular induction of immune modulation or tissue regeneration rather than cell replacement and is, therefore, amenable to investigator-sponsored studies given the low cost and minimal technical capabilities required for the trials. One area of active research has been the application of autologous human MSCs for acute myocardial infarction, where cells are delivered directly to the ischemic cardiac tissue. Numerous trial designs have resulted in hundreds of patients being treated to date. The meta-analysis from collective clinical data suggest MSCs show a modest, yet significant, improvement in functional markers, such as left ventricular ejection fraction (LVEF), with reduction in left ventricular end-systolic volume and lesion area (reviewed in Abdel-Latif et al., 2007, Martin-Rendon et al., 2008). Therefore, the data suggest that autologous stem cell therapy in cardiac disease results in improved cardiac functioning outcomes. However, the field will need more adequately powered, randomized trials to demonstrate clinical outcomes (e.g., mortality benefit) and extended clinical assessments of patient outcomes in order to become a standard of care. As autologous stem cell therapy becomes a reliable treatment in ischemic, inflammatory, or autoimmune diseases, biopharmaceutical companies will evaluate business models to determine the commercial opportunity associated with investment.

Table 2. Current Pipeline of Cell-Based Therapies in Development

Clinical Phase[a]	Cell-Based Therapies	Company-Sponsored Therapies	Proportion of Company-Sponsored Therapies (%)	Large Company-Sponsored Therapies
Phase I	38	35	92	0
Phase II	24	22	92	3 (Teva, Baxter, Genzyme)
Phase III	6	5	83	0
Total	68	62	91	3 (5%)
Disease-Specific View[b]				
Disease	Trials	Company Sponsored Trials	Proportion of Company Sponsored trials (%)	Large Companies
Cardiac Disease	117	24	20	1 (Baxter)
Autoimmune Disorders	60	6	10	1 (Genzyme)
Endocrine/Metabolic	43	11	26	1 (Genzyme)
CNS	43	7	16	0
Total	263	48	18%	1%

[a] ADIS Insight database search using cell replacement therapy as the search parameter with Phase I/II trials put in Phase I bucket and Phase II/III trials placed in Phase II bucket.
[b] From clinicaltrials.gov. Search parameters used were "Cardiac Stem Cell," "Autoimmune Stem Cell," "Endocrine Stem Cell," and "Nervous System Stem Cell" with additional parameters of "NOT tumor," "NOT cancer," and "NOT proliferative disorder" used to winnow out oncology-related trials.

In health economic terms, autologous cell-based therapies can be cost effective. For example, a recent analysis of stem cell-derived bladder replacement in the UK demonstrated a cost benefit of £36,000 over existing therapies. Creating therapies for each individual is a very different business from pharma's normal operating model, in that each patient becomes a lot of 1 and entails significant logistical challenges (Smith, 2009). Companies considering this opportunity will need to evaluate if there are sufficient patients requiring one cell replacement to develop a scaleable process. Two feasible commercial approaches to autologous cell therapy have been taken: a centralized and distributed model. Tigenix have developed a centralized cell production approach for ChondroCelect, an approved therapy for cartilage repair in Europe. A centralized model requires patients to travel to a specialized center for treatment. An alternative is the distributed model, in which cells are removed from patients and isolated locally by means of a device before being reintroduced to the patient. In this model, patients are treated on site and are not required to travel to a specific dedicated center for treatment. The Cytori Celution device allows bedside isolation of mesenchymal stem/stromal cells derived from adipose tissue following liposuction. These cells are then available for readministration to patients for cosmetic and reconstructive surgery in Europe and Asia. Cytori's autologous MSCs are also in clinical trials for autologous treatment of acute and chronic heart disease. This organization recently partnered with GE Healthcare for the distribution of the Celution devices and commercialization of stem cell banking and research markets. Even if a significant proportion of the registered autologous stem cell clinical trials underway/completed show efficacy, several hurdles must be overcome to bring this approach into pharma's commercial sphere. Closed-loop devices (sterile, transportable, single-use production units) that simplify cell isolation and expansion and preclude using costly GMP facilities may be necessary. Evidence that efficacy and/or safety profiles are superior to existing traditional small molecule or biologic therapies will be required to justify the likely high cost of goods and the subsequent selling price. Regulatory oversight will depend on the level of manipulation (e.g., drug treatment, expansion, etc.) of the autologous cells. Nevertheless, recognition that future opportunities exist in this area is evidenced by licensing and investment by biopharmaceutical companies (Table 1).

Human adult and umbilical/placental-derived stem cell sources are being developed as allogeneic cell-based therapies. Current allogeneic stem cell-based approaches are not typically designed to engraft and rely on a variety of mechanisms to deliver efficacy, including secretion of paracrine factors prior to immune destruction. Therefore, the mechanism of action is not dissimilar to autologous approaches. There are, however, data that suggest that human MSCs may not illicit an allogeneic immune response when delivered therapeutically (Klyushnenkova et al., 2005). Therefore, the potential exists to treat thousands of patients with expanded adult stem cells from a single donor. True replacement and integration using allogeneic cells will require re-education of the host's immune system, some type of immune suppression treatment, or HLA matching prior to treatment. Treatment with immunosuppressive therapy can be done today but is not a preferred option, while the other options do not seem likely in the short term. A robust understanding of the therapeutic areas where adult progenitor cells have clinical efficacy is likely to emerge over the next few years. The majority of studies being pursued in the clinical trials database use mesenchymal stem cells or multipotent adult progenitors for treatment of immune disorders, given their anti-inflammatory and immune-modifying properties (reviewed in Uccelli et al., 2008). Although adult stem cell approaches have been documented as safe thus far, further studies using human adult stem cells will be required to demonstrate efficacy in immune or

inflammatory conditions. While promising data has been reported (albeit only in press releases) by Osiris/Genzyme for multiple indications, including GvHD, this and other partnerships (e.g., Pfizer/Athersys in inflammatory bowel disease) will help define the opportunity for adult allogeneic cell therapy. In terms of stimulating wound repair and treating critical limb ischemia and myocardial infarction, as with autologous cell trials, modest benefits have already been observed, and many others studies have yet to conclude. As a business model, allogeneic cell sources are more aligned with the pharmaceutical business practice of centralized product production and distribution to health care providers. However, for pharma to aggressively adopt allogeneic adult cell therapy, multiple issues will need to be addressed, including cell expansion and manufacturing, product consistency, product delivery to the patient, and successful well-designed, well-controlled clinical trials showing significant benefits over standard of care. Given that cell-based therapies are already available (e.g., Apligraf from Organogenesis), this set of challenges is not insurmountable but will require additional investment to minimize the cost of making the cell therapy and providing it routinely at the point of care.

Direct involvement from pharma in human ESC therapy has been modest. Concerns regarding the use of a human ESCs notwithstanding, there are advantages of using pluripotent stem cells as source material for therapy because all cell types are theoretically possible for expansion and use in cell replacement therapies. Examples include the encapsulated beta-cells for treatment of type 1 diabetes as proposed by ViaCyte (formerly Novocell) and supported by J&J's equity stake, Geron's oligodendrocyte therapy for spinal cord injury, and Pfizer's collaboration with University College London to produce retinal pigment epithelium for the treatment of age-related macular degeneration. Concerns around safety, anticipated regulatory complexity, and lack of experience in this new area of research may be significant barriers to entry. While iPSCs may remove ethical concerns, the safety and regulatory hurdles remain undiminished and may even be greater. Much research needs to be done to show that the myriad of ways of generating iPSCs do everything that the gold standard of hESCs do—and no more—but the data have thus far been mixed (Rowntree and McNeish, 2010).

Conclusion

Commercially, any approach can be viable if two major hurdles are overcome: overall cost of the product and significant patient-benefits. As payers implement more rigorous health economic analysis in decision-making, truly restorative or disease-modifying therapies will offer greater value and subsequent reimbursement value over palliative ones. Cell-based therapies move us toward this goal, although currently launched products (e.g., Dermatology and Orthopaedic focused) have been limited commercially due to their inability to show significant efficacy benefits over standard of care, particularly as related to the costs of cell-based therapies relative to the cost of standard of care. pharma is moving gradually into stem cells, first using tools for traditional drug discovery, enhanced by the greater availability of cell types through iPSC technology. The opportunity to generate novel molecules that modify endogenous stem cells is very much in scope and will likely lead to new therapeutic approaches using small molecules and biologics to enhance the body's natural repair mechanisms. These are near-term options and need little change in the way that pharmaceutical industry works today. The move to true cell-based therapeutics by pharma is still modest. Some companies have preferred to take equity stake in active biotech companies while others are adopting a "watchful waiting" approach until the myriad of clinical trials currently underway read out definitively one way or another before actively investing in the space. As there are hundreds of regenerative medicine-focused biotechnology companies globally, it is expected that partnerships with biopharmaceutical companies will develop following the demonstration of clinically safe and efficacious approaches. Pfizer and Teva have taken a much more proactive "partner and learn" approach, and it is highly likely that some companies may have stealth efforts that are not yet visible in the public domain. We still do not know whether regenerative medicine will provide niche benefit or will revolutionise healthcare. If the latter, pharma needs to be prepared for investment and change. Should significant benefit be demonstrated by stem cell-based medicine, one must anticipate a flurry of acquisitions and partnering deals to make way for the future.

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